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REVIEW OF THE DOCTORAL DISSERTATION BY JOSEPH DANIEL GBUBELE

"Asymmetric synthesis of α-substituted phosphonates and phosphonic acids via hydrophosphonylation of substrates containing carbon- heteroatom bond with TADDOL-derived H-phosphonate"

Mr. Joseph Daniel Gbubele carried out his doctoral studies under the guidance of Professor Tomasz Olszewski at Wroclaw Technical University in Faculty of Chemistry.

The importance of undertaken studies

The asymmetric synthesis maintains high significance in organic and medicinal chemistry. It is a common knowledge that chirality considerably affects the biological activity of organic compounds. Author took an interest in organophosphorus compounds, elaborating synthetic strategies to obtain their α-substituted analogs in stereochemically enriched form.

Characteristic and comments to the thesis

The doctoral dissertation consists of 257 pages and impressive number of references, 315, which indicates Author's vast knowledge about the respective field. The thesis starts with an abstract, acknowledgements, table of contents, and the latter is followed by the 40 pages long literature part, which recognizes the importance of aminophosphonic and aminophosphinic acids, as biologically active compounds as well as additives in the organic synthesis. The second part of this chapter is devoted to the applications of organophosphorus compounds bearing chiral auxiliary, such as TADDOL, BINOL and menthyl in diverse reactions, including Michael addition and hydrophosphonylation of imines and aldehydes. Author also sketches the state-of-the-art of the field directly linked to his studies, meaning application in the synthesis of selected *H*-phosphonates bearing ester chiral auxiliary. For analogs functionalized with TADDOL, Author concisely introduces the work done in the group of his supervisor, Prof. Olszewski. The final part,

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page 50-51, constitutes interesting compilation of the presented knowledge about the selected phosphonates bearing chiral auxiliaries. It would be valuable to hear during the defense, how Author summarizes how/ if his developments addressed the challenges of the field defined on page 51 of the thesis.
The research part starts on page 55 and is divided into four chapters (these four parts are literally named "chapters" as the only ones in the thesis) followed by experimental part and references. I found the way this part was presented slightly confusing. For example, chapter number 1.0 appears in the thesis nine times, making my work as a reviewer harder, e.g. when I am trying to refer to certain sections. Happily, schemes and numbering of compounds is continuous throughout the whole dissertation. Also, each chapter, which should be devoted to the research part, contains both, author's studies and literature background, in similar volume, which in my opinion affects clarity of presentation. Experimental part contains synthetic details on how the compounds were obtained. Throughout the work Author used the NMR spectroscopy to determine conversion and stereochemical outcome of the reaction, which in selected cases was appropriately supported by X-ray studies and measurements of optical rotation of the deprotected analogs.

Below, I will shortly refer to each chapter separately, referring to one of the main characters of this work, TADDOL-derived *H*-phosphonate, by its number **29**, used throughout the thesis.

Chapter 1 author starts with introductory part on the synthetic use of α-amido sulphones. The second part constitutes the text on their use in asymmetric hydrophosphonylation. Author synthesized 18 racemic α-aminophosphonates, with diverse ester groups on phosphorus and 12 TADDOL-phosphonates with excellent (in 9 out of 12 cases) diastereoselectivities. Simultaneously, Author proved that stereochemical outcome of the reaction can be controlled by the stereochemistry of the TADDOL auxiliary.
Summarizing this part on page 84, Author makes the following claim: "I have demonstrated that the α-amido sulphones are readily accessible as stable substitutes for imines". It might be just the problem of the foreign language used in the thesis that it seems like the potential of α-amido sulphones was discovered by the presented work. As a matter of fact, it has been already proven in the past.

Chapter 2 is devoted to hydrophosphonylation of *N*-substituted imines. The highest degree of transformation was obtained for aldimines. In the case of ketone analogs low yields were observed, despite optimization attempts. While studying the possibility of increasing the diastereoselectivity of the reaction by creating imine *in situ,* Author observed formation of the mixture of products, amino- and hydroxyphosphonates. Interestingly, hydroxyphosphonates were obtained with high diastereomeric ratio (93/7), constituting the starting point for the studies in the following chapter.

In **Chapter 3** Author concentrates on asymmetric hydrophosphonylation of carbonyl compounds. In the introduction Author shows many possible transformations of α-

hydroxyphosphonates and it is hard not to agree with their utilitarian character in the synthesis. However, direct transformation of hydroxy analog into aminophosphonates is not trivial. The only reference given here (number 247, Keglevich and collaborators *Synthesis of α-aminophosphonates from α-hydroxyphosphonates; a theoretical study. Heteroatom. Chem.*, **2016**, *27*, 260), turns out to be theoretical work, with some experiments showing the possibility of MW-assisted substitution of the hydroxy analogs with primary amines. I would like to encourage the doctoral candidate to comment on how common this method is and what other methods of creating α-amino phosphonates from their hydroxy analogs are popular.

In this part of the doctorate, Author worked on improving the method, previously reported by the group of Supervisor, of asymmetric synthesis of α-hydroxyphosphonates. By using the observation described in Chapter 2, Author proposed the use of amine (1 eq benzhydryl amine), toluene, low temperature and 30-60 h. The diastereoselectivities thus obtained were good to excellent, and upon purification the dr could be improved. Author decided to further optimize the conditions and used catalytic amount of chiral amine (20% quinine, rt, 24 h, toluene). However, when comparing the results from the first and the second approach (schemes 94 and 95), it is not clear what advantage was given by the application of the chiral base. I would like the Author to comment on that point during defense.

Author tried to adapt the developed conditions to hydrophosphonylation of ketones, additionally running optimization studies (20 conditions tested) on the example of acetophenone. However, due to limited success (the highest conversion was 63% and dr was oscillating around 75:25) he reasonably did not check the scope of this reaction.

Author showed through X-ray analysis, that the newly formed chirality center is determined by the stereochemistry of chiral auxiliary in **29**, which conveniently makes accessible both stereoisomers.

I would like to highlight here that Author optimized several methods of synthesis of α-substituted phosphonates, in this and other chapters, achieving good to excellent results in terms of asymmetric induction for multiple examples. What I am lacking most in this dissertation is the scarcity of mechanistic considerations/ models, explaining the observed stereochemical outcome. It seems to be proposed only in Chapter 3, Figure 30, page 146, and rather refers to the role of a chiral base, while schemes 94 and 95 show similar outcomes for both strategies, with and without the use of chiral amine, indicating that the major role is played here by chirality of **29**. I would like the Author to comment on that point during the defense.

In **Chapter 4** Author describes his studies on the utility of hydrazones, such as reductive coupling of *N*-tosyl hydrazones with compound **29** and hydrophosphonylation of *N*-acyl hydrazones with **29**. While the first reaction led to reaction with low diastereoselectivities, in the reaction with *N*-acyl hydrazones Author managed to obtain higher values of dr, compared with literature report of Herrera and collaborators, who carried out studies on achiral phosphorus analogs. In most cases Author obtained high dr (~85:15), which were improved upon column chromatography or crystallization. When trying to apply one-pot

approach, meaning *in situ* generation of hydrazone, Author mainly obtained the hydroxyphosphonate analog.
As in the comment already contained in the previous paragraphs of this review, I would like to ask Mr Gbubele to describe the role of cinchonine-**I** in the reaction compared with the role of TADDOL auxiliary. The entries 3 and 7 in Table 14 (page 165) show, there was only slight increase of asymmetric induction, compared with conditions without the use of chiral base. Secondly, as is shown in entry 5 of the same Table, when using another chiral base, quinine-**III**, the reverse diastereomeric preference was observed, showing the potential of this approach to obtain in excess product with opposite chirality. I found this result valuable, but I did not find comment on that in the thesis. Maybe it is because of the fact, that similar outcome could be achieved when (*S,S*)-**29** was used in the reaction.

I would also like to draw the Author's attention to a few additional points:
a) When dr is 50:50, I would recommend to not call it "significantly low" (see p. 42) or "poor" (p. 113, Table 8, entry 1). It was rather "none".
b) Author starts chapter 4 explaining the significance of hydrazones, showing multiple examples of *biologically active compounds bearing the hydrazone scaffold* in Fig. 31 (p. 151). However, in the text under this figure, it is claimed that hydrazone are precursors of compounds with biological activities, referring to compounds from Fig. 31. Please specify, which claim is correct.
c) In experimental section I did not notice the information about the synthesized compounds in terms of their existence in the literature. How many compounds are new and how many have been synthesized previously?

Summary

Mr. Joseph Daniel Gbubele co-authors three publications. Surely, not all obtained results have been published yet. One publication was not reported as a part of graduate studies, but as a result of fruitful doctoral scholarship at Aarhus University in Denmark. The thesis contains experimental material, in which Author elaborated methods of the synthesis of α-substituted organophosphorus esters, in some cases achieving excellent diastereoelectivities, with the possibility to control the stereochemical outcome by changing the chirality of TADDOL auxiliary on phosphorus moiety.

I conclude that Mr. Joseph Daniel Gbubele correctly selected the research topic, clearly formulated the purpose of the work, planned and performed the experiments well, demonstrated the ability to interpret and discuss the results. The doctoral thesis submitted for review is a valuable contribution to the existing state of knowledge, and it meets the statutory conditions for doctoral dissertations. Therefore, I am submitting an application to the Scientific Council of the Discipline of Chemical Sciences of the Wrocław University of Science and Technology to admit the PhD student to the next stages of the doctoral process.